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=> D HIS

     (FILE 'HOME' ENTERED AT 17:22:44 ON 20 JUN 2006)

     FILE 'STNGUIDE' ENTERED AT 17:22:56 ON 20 JUN 2006

     FILE 'MEDLINE' ENTERED AT 17:23:07 ON 20 JUN 2006
L1         24868 S GH OR GROWTH HORMONE! OR SOMATOTROPIN! OR SOMATOTROPHIN!
L2        227469 S HYPOXI! OR ISCHEMI!
L3           144 S L1 AND L2
L4          2955 S L1 AND NEURO?
L5          2933 S L4 NOT L3
L6            72 S L5 AND (RESCUE? OR PROTECT? OR PROPHYL?)
L7           532 S L5 AND (CNS OR BRAIN)
L8           518 S L7 NOT L6

=>
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5,958,933 9/28/99
filed 6/6/95
column 142, line 13-15

WO 2001-JP10416
JP 2000-367183

#256 6,121,416 - 1997

#237 - date?
6469024 5/10/01
5/11/00 provisional
MS + GH secretion

#236 ~~6,352,982~~
WO 98/42882
10/29/98

=> D BIB AB 1-9

L12 ANSWER 1 OF 9 MEDLINE on STN
AN 2005240737 MEDLINE
DN PubMed ID: 15879686
TI Treatment in animal models.
AU Guan J; Bennet L; Gluckman P D; Gunn A J
CS The Liggins Institute, Faculty of Medicine and Health Sciences, The
University of Auckland, Auckland, New Zealand..
j.guan@auckland.ac.nz
NC R01 HD-32752 (NICHD)
SO Endocrine development, (2005) Vol. 9, pp. 31-43. Ref: 27
Journal code: 101138956. ISSN: 1421-7082.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200507
ED Entered STN: 10 May 2005
Last Updated on STN: 9 Jul 2005
Entered Medline: 8 Jul 2005
AB It is now well established that neurons and other cell types may die many
hours or even days after hypoxic-ischemic injury due to activation of
programmed cell death (apoptotic) pathways. The potent anti-apoptotic
factor IGF-1 and its binding proteins and receptors are intensely induced
within damaged brain regions following brain injury suggesting a possible
a role for IGF-1 in endogenous brain recovery. Exogenous administration
of IGF-1 within a few hours after brain injury has now been shown to be
protective in both grey and white matter, and leads to improved long-term
neurological function. The limited window of opportunity for treatment
with IGF-1 can be extended by spontaneous mild post-hypoxic hypothermia,
probably due to delayed evolution of apoptotic processes. The efficacy of
IGF-1 is specific to particular cellular phenotypes and brain regions, and
its neuroprotective effects are mediated by IGF-1 receptors and binding
proteins. Intriguingly its naturally cleaved N-terminal tripeptide (
glycine - ***proline*** - ***glutamate*** , ***GPE***) has
been demonstrated to be neuroprotective after both central and peripheral
administration. Peripheral administration of ***GPE*** also prevents
the loss of dopamine neurons and improves long-term functional recovery
following 6-OHDA lesion. However, ***GPE*** is unlikely to contribute
significantly to the direct effects of IGF-1.

L12 ANSWER 2 OF 9 MEDLINE on STN
AN 2005123223 MEDLINE
DN PubMed ID: 15752541
TI Central penetration and stability of N-terminal tripeptide of insulin-like
growth factor-I, ***glycine*** - ***proline*** - ***glutamate***
in adult rat.
AU Baker A M; Batchelor D C; Thomas G B; Wen J Y; Rafiee M; Lin H; Guan J
CS Liggins Institute, Faculty of Medical and Health Science, The University
of Auckland, Private Bag 92019, Auckland, New Zealand.
SO Neuropeptides, (2005 Apr) Vol. 39, No. 2, pp. 81-7. Electronic
Publication: 2005-01-28.
Journal code: 8103156. ISSN: 0143-4179.
CY Scotland: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200505
ED Entered STN: 9 Mar 2005
Last Updated on STN: 6 May 2005
Entered Medline: 5 May 2005
AB Insulin-like growth factor-I is a neurotrophic factor and can prevent
neurons from ischemic brain injury. However, the large molecular weight
and metabolic effects can be problematic in its central delivery.
Glycine - ***proline*** - ***glutamate*** (***GPE***) is
the N-terminal tripeptide of insulin-like growth factor-I, which is
naturally cleaved in the plasma and brain tissues. ***GPE*** reduces
neuronal loss from hypoxic-ischemic brain injury following central
administration. Central penetration and the stability of ***GPE*** in
the plasma and central nervous system were examined in rats using
radioimmunoassay and HPLC. ***GPE*** was rapidly metabolised in the
plasma (8 min) after intraperitoneal administration. Despite having a
short half-life in plasma, ***GPE*** was detected in the cerebrospinal
fluid up to 40 min after intraperitoneal administration. With present of
peptidase inhibitors, ***GPE*** existed in the brain tissue up to 3 h
after intracerebroventricular administration, suggesting a role for
peptolysis in its stability. The endopeptidase inhibitors 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF) reduced
GPE metabolism in the brain tissue while acid peptidase inhibitor
pepstatin-A decreased ***GPE*** metabolism in the plasma. ***GPE***
reduced neuronal loss in the CA1-2 sub-region of the hippocampus given
(intraperitoneally) after 30 min of hypoxic-ischemic injury in adult rats,
further suggested the effectiveness of ***GPE*** central uptake.
These results indicated that ***GPE*** crosses the blood-CSF and the
functional CSF-brain barriers. The longer half-life of ***GPE*** in
the CNS may be due to its unique enzymatic stability.

L12 ANSWER 3 OF 9 MEDLINE on STN

AN 2004556945 MEDLINE
DN PubMed ID: 15527823
TI Neuroprotective effects of the N-terminal tripeptide of insulin-like
growth factor-1, ***glycine*** - ***proline*** - ***glutamate*** (
GPE) following intravenous infusion in hypoxic-ischemic adult
rats.
AU Guan J; Thomas G B; Lin H; Mathai S; Bachelor D C; George S; Gluckman P D
CS The Liggins Institute, Faculty of Medical and Health Sciences, University
of Auckland, Private Bag 92019, 2-6 Park Avenue, Grafton, Auckland, New
Zealand.. j.guan@auckland.ac.nz
SO Neuropharmacology, (2004 Nov) Vol. 47, No. 6, pp. 892-903.
Journal code: 0236217. ISSN: 0028-3908.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200501
ED Entered STN: 6 Nov 2004
Last Updated on STN: 14 Jan 2005
Entered Medline: 13 Jan 2005
AB The N-terminal tripeptide of insulin-like growth factor-1, ***GPE***
is neuroprotective when given intracerebroventricularly 2 h after
hypoxic-ischemic (HI) brain injury in rats. We have now examined whether
GPE can cross the blood-brain barrier and exert neuroprotective
actions following intravenous administration. Following a single bolus
intravenous injection, ***GPE*** was rapidly metabolized and cleared
from the circulation. The short half-life (<2 min) in blood was
subsequently associated with modest and inconsistent neuroprotection. In
contrast, potent neuroprotection of ***GPE*** was consistently
observed in all brain regions examined following 4 h intravenous infusion
(12 mg/kg). The neuroprotective effects of ***GPE*** after infusion
showed a broad effective dose range (1.2-120 mg/kg) and an extended window
of treatment to 7-11 h after injury. The central penetration of
GPE after intravenous infusion was injury-dependent. ***GPE***
also improved long-term somatofunction with a comparable neuronal outcome.
GPE reduced both caspase-3-dependent and -independent apoptosis in
the hippocampus. Treatment with ***GPE*** also inhibited microglial
proliferation and prevented the injury-induced loss of astrocytes. In
conclusion, the neuroprotective actions of ***GPE*** infusion were
global, robust and displayed a broad effective dose range and treatment
window. ***GPE*** 's activity included the prevention of neuronal
apoptosis, promotion of astrocyte survival and inhibition of microglial
proliferation. With injury specific central penetration, ***GPE***
has considerable promise as a systemic neuroprotective treatment after
acute encephalopathies.

L12 ANSWER 4 OF 9 MEDLINE on STN
AN 2003576269 MEDLINE
DN PubMed ID: 14656520
TI Pharmacokinetics of ***glycine*** - ***proline*** - ***glutamate***
, the N-terminal tripeptide of insulin-like growth factor-1, in rats.
AU Batchelor D C; Lin H; Wen J-Y; Keven C; Van Zijl P L; Breier B H; Gluckman
P D; Thomas G B
CS NeuronZ Ltd, PO Box 9923, Newmarket, Auckland 1031, New Zealand..
david.batchelor@neuronz.com
SO Analytical biochemistry, (2003 Dec 15) Vol. 323, No. 2, pp. 156-63.
Journal code: 0370535. ISSN: 0003-2697.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200408
ED Entered STN: 16 Dec 2003
Last Updated on STN: 1 Sep 2004
Entered Medline: 31 Aug 2004
AB ***Glycine*** - ***proline*** - ***glutamate*** (***GPE***) is
the N-terminal tripeptide of insulin-like growth factor-1 and has been
shown to be neuroprotective following ischemia-induced brain injury. The
pharmacokinetics of ***GPE*** were studied in adult rats since
GPE is a candidate for use in neuroprotection therapies. To
measure plasma concentrations of ***GPE*** a novel radioimmunoassay
was developed whereby ***GPE*** was initially derivatized with Bolton
and Hunter reagent before use in a standard homologous assay against the
Bolton and Hunter iodinated form. The derivatized ***GPE***
radioimmunoassay showed a 83% recovery of unlabeled ***GPE*** and
complete parallel displacement with rat plasma. The simplicity and speed
of the assay described here indicate an exciting new use for a previously
described technology. The pharmacokinetic studies were conducted in adult
rats using a single bolus intravenous injection of ***GPE*** at 30 or
100 mg/kg and showed that ***GPE*** was rapidly cleared from the
circulation. In addition, evidence of the route of the metabolic
degradation of ***GPE*** is presented. The findings presented here
are the first description of the pharmacokinetics of ***GPE*** and
suggest that, because of its very short half-life in plasma, continuous

intravenous infusion of ***GPE*** may be the preferred route of
administration for use in future neuroprotection therapies.

L12 ANSWER 5 OF 9 MEDLINE on STN
AN 2002046495 MEDLINE
DN PubMed ID: 11730700
TI Neuroprotective effects of the N-terminal tripeptide of IGF-1,
glycine - ***proline*** - ***glutamate*** , in the immature rat
brain after hypoxic-ischemic injury.
AU Sizonenko S V; Sirimanne E S; Williams C E; Gluckman P D
CS Liggins Institute, Faculty of Medicine and Health Science, The University
of Auckland, Private Bag 92019, Auckland, New Zealand..
stephane.sizonenko@medicine.unige.ch
SO Brain research, (2001 Dec 13) Vol. 922, No. 1, pp. 42-50.
Journal code: 0045503. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 24 Jan 2002
Last Updated on STN: 20 Feb 2002
Entered Medline: 19 Feb 2002
AB Insulin growth factor 1 (IGF-1) has an important role in brain development
and is strongly expressed during recovery after a hypoxic-ischemic injury.
Some of its central actions could be mediated through the N-terminal
tripeptide fragment of IGF-1: Gly-Pro-Glu (***GPE***). The
neuroprotective properties of ***GPE*** given after a moderate injury
in the developing rat brain were evaluated and the binding sites of [(3)H]
GPE characterised by autoradiography. After right unilateral
injury, ***GPE*** or vehicle (V) was injected in the right lateral
ventricle (i.c.v.) or in the peritoneal cavity (i.p.) of 21-day-old rats.
The percentage of surviving neurons in CA1-2 of the hippocampus was higher
in the animals treated with 30 microg of ***GPE*** i.c.v. (V:
7.7+/-4.9%, ***GPE*** : 26.4+/-7.5%, P=0.02) and 300 microg i.p. (V:
30.2+/-9.1%, ***GPE*** : 68.8+/-10.6%, P=0.02) than in animals
receiving vehicle. I.p. injection of 300 microg of ***GPE*** (V:
78.4+/-7.5%, ***GPE*** : 88.4+/-3.2%, P=0.04) was also neuroprotective
in the lateral cortex. I.c.v. injection of [(3)H] ***GPE*** suggested
binding to glial cells in the white matter tracts, the cortex and striatum
as opposed to neurons. Although the precise mode of action of ***GPE***
is unknown, this study suggests that local administration of ***GPE***
is neuroprotective after brain HI injury via glial cells. In addition,
systemic administration of ***GPE*** showed a more widespread
neuroprotective effect. ***GPE*** may represent a complementary
pathway for central and systemic IGF-1's antiapoptotic effects.

L12 ANSWER 6 OF 9 MEDLINE on STN
AN 2001177905 MEDLINE
DN PubMed ID: 11202225
TI A role for the somatotropic axis in neural development, injury and
disease.
AU Scheepens A; Williams C E; Breier B H; Guan J; Gluckman P D
CS Research Centre for Developmental Medicine and Biology, Faculty of Medical
and Health Science, University of Auckland, New Zealand..
a.scheepens@auckland.ac.nz
SO Journal of pediatric endocrinology & metabolism : JPEM, (2000) Vol. 13
Suppl 6, pp. 1483-91. Ref: 78
Journal code: 9508900. ISSN: 0334-018X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 4 Apr 2001
Last Updated on STN: 4 Apr 2001
Entered Medline: 29 Mar 2001
AB This review article discusses the roles of the somatotropic axis in the
growth and development of the normal central nervous system (CNS) and
during recovery from brain injury. Classically, the actions of
pituitary-derived growth hormone (GH) have been reported to be primarily
mediated via the induction of hepatic insulin-like growth factor-I
(IGF-I). GH receptors (GHRs), however, have now been identified in many
body tissues and shown to have both endocrine and local actions, some of
which are IGF-I independent. Within the brain, GHRs are widely located
across a range of cellular phenotypes, yet little is known regarding their
function or endogenous ligand. It is now becoming accepted that GH, like
IGF-I, is integrally involved in the growth and development of the normal
CNS. Following brain injury, IGF-I mRNA is induced, primarily within
reactive microglia. The resultant IGF-I protein appears to have a dual
role, first as an endogenous neurotropic and anti-apoptotic agent acting
directly on stressed cells, and second as a prohormone for generation of
the N-terminal tripeptide of IGF-I, ***glycine*** - ***proline*** -
glutamate (***GPE***), and the resulting des-N-(1-3)-IGF-I,
both of which have specific neuroprotective properties. Our work on
deciphering the upstream regulators of injury-induced IGF-I has revealed
that a GH-like substance is strongly upregulated after brain injury and

specifically associated with stressed neurons and glia. Subsequent to
this finding, GH administered centrally 2 hours after a hypoxic-ischemic
brain injury in juvenile rats was found to provide significant
neuroprotection, interestingly, in a spatiotemporal pattern distinct from
the neuroprotection offered by IGF-I. The implications of these findings
in regard to the growth, development and injury response of the CNS are
discussed.

L12 ANSWER 7 OF 9 MEDLINE on STN
AN 2000185378 MEDLINE
DN PubMed ID: 10719076
TI N-terminal tripeptide of IGF-1 (***GPE***) prevents the loss of TH
positive neurons after 6-OHDA induced nigral lesion in rats.
AU Guan J; Krishnamurthi R; Waldvogel H J; Faull R L; Clark R; Gluckman P
CS Research Center for Developmental Medicine, School of Medicine, University
of Auckland, Private Bag 92019, Auckland, New Zealand..
j.guan@auckland.az.nz
SO Brain research, (2000 Mar 24) Vol. 859, No. 2, pp. 286-92.
Journal code: 0045503. ISSN: 0006-8993.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
ED Entered STN: 18 May 2000
Last Updated on STN: 18 May 2000
Entered Medline: 9 May 2000
AB The effect of the N-terminal tripeptide of insulin-like growth factor
(IGF)-1, ***glycine*** - ***proline*** - ***glutamate*** (***GPE***), as a neuroprotective agent for nigro-striatal dopaminergic
neurons was examined in the present study using a rat model of Parkinson's
disease. A unilateral nigro-striatal lesion was induced in rats by
injecting 6-hydroxydopamine (6-OHDA) into the right medial forebrain
bundle (MFB). ***GPE*** (3 microgram) or its vehicle was administered
intracerebroventricularly (i.c.v.) 2 h after the 6-OHDA lesion.
Tyrosine-hydroxylase (TH) immunohistochemistry in the substantia nigra
compacta (SNc) and the striatum were examined 2 weeks after the lesion.
Following 6-OHDA injection, the number of TH immunopositive neurons in the
ipsilateral SNc was reduced. The density of TH immunostaining was also
reduced in the ipsilateral SNc and the striatum. Treatment with a single
dose of ***GPE*** (n=9) significantly prevented the loss of TH
immunopositive neurons (p<0. 001) and restored the TH immunoreactivity in
both the SNc and the striatum compared with the vehicle control group
(n=9, p<0.001). The results suggest that ***GPE*** showed promise as
a potential treatment for Parkinson's disease.

L12 ANSWER 8 OF 9 MEDLINE on STN
AN 1999417601 MEDLINE
DN PubMed ID: 10486177
TI The IGF-I amino-terminal tripeptide ***glycine*** - ***proline*** -
glutamate (***GPE***) is neuroprotective to striatum in the
quinolinic acid lesion animal model of Huntington's disease.
AU Alexi T; Hughes P E; van Roon-Mom W M; Faull R L; Williams C E; Clark R G;
Gluckman P D
CS School of Medicine, University of Auckland, Auckland, New Zealand..
t.alexi@auckland.ac.nz
SO Experimental neurology, (1999 Sep) Vol. 159, No. 1, pp. 84-97.
Journal code: 0370712. ISSN: 0014-4886.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 14 Oct 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 7 Oct 1999
AB Huntington's disease is an incurable genetic neurological disorder
characterized by the relatively selective degeneration of the striatum.
Lesioning of the striatum in rodents using the excitatory amino acid
agonist, quinolinic acid (QA), effectively mimics the human neuropathology
seen in Huntington's disease. Using this animal model of Huntington's
disease, we investigated the ability of the insulin-like growth factor-I
(IGF-I) amino-terminal tripeptide ***glycine*** - ***proline*** -
glutamate (***GPE***) to protect striatal neurons from
degeneration. Adult rats received a single unilateral intrastriatal
injection of QA (100 nmol) and then daily injection of either vehicle or
GPE (0.3 microgram/microliter/day) into the striatum for 7 days.
QA at this dose resulted in a partial lesioning of the striatum after 7
days to approximately 50% of cells of unlesioned levels in vehicle-treated
animals. The major striatal neuronal phenotype, GABAergic projection
neurons, were identified by immunocytochemical labeling of either
glutamate decarboxylase 67 (GAD(67)) or the calcium binding protein
calbindin in alternate sections. Treatment with ***GPE*** for 7 days
reversed the loss in projection neurons when assessed by counts of
calbindin-stained cells; however, these rescued cells did not regain
immunologically detectable levels of GAD(67). ***GPE*** also
significantly reversed the phenotypic degeneration of cholinergic
interneurons identified by immunolabeling for choline acetyltransferase

(ChAT) and NADPH diaphorase interneurons identified histochemically.
GPE treatment failed to rescue the calcium binding protein
interneuron populations of parvalbumin and calretinin neurons. These
findings reveal that exogenous administration of ***GPE*** selectively
prevents excitotoxin induced phenotypic degeneration of striatal
projection neurons and cholinergic and NADPH diaphorase interneurons in an
animal model of Huntington's disease.

L12 ANSWER 9 OF 9 MEDLINE on STN
AN 1999191943 MEDLINE
DN PubMed ID: 10094155
TI Neuroprotective effects of Gly-Pro-Glu, the N-terminal tripeptide of
IGF-1, in the hippocampus in vitro.
AU Saura J; Curatolo L; Williams C E; Gatti S; Benatti L; Peeters C; Guan J;
Dragunow M; Post C; Faull R L; Gluckman P D; Skinner S J
CS Department of Pharmacology, School of Medicine, University of Auckland,
New Zealand.
SO Neuroreport, (1999 Jan 18) Vol. 10, No. 1, pp. 161-4.
Journal code: 9100935. ISSN: 0959-4965.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 7 Jun 1999
Last Updated on STN: 7 Jun 1999
Entered Medline: 25 May 1999
AB Insulin-like growth factor 1 (IGF-1) plays a critical role in CNS
development. IGF-1 can block neuronal apoptosis in vitro and in vivo.
IGF-1 is thought to be cleaved into des-N-(1-3)-IGF-1 and an amino
terminal ***glycine*** - ***proline*** - ***glutamate*** (***GPE*** tripeptide). Here we report a neuroprotective role for
GPE tripeptide, with enhanced survival of the CA1-2 hippocampal
neurons following an excitotoxic insult in vitro. Binding and
displacement studies suggest uniquely distributed sites of action within
the rat including the hippocampal CA1-2, pyriform cortex, amygdala,
choroid plexus, blood vessels and to a lesser extent in the cortical
regions. A similar pattern of binding was seen in the human. This
finding could lead to new strategies to reduce neuronal death after injury
and in disease.

=> D HIS

(FILE 'HOME' ENTERED AT 20:42:27 ON 14 JUN 2006)

FILE 'MEDLINE' ENTERED AT 20:42:36 ON 14 JUN 2006
L1 24174 S GH
L2 485 S GPE
L3 1 S L1 AND L2
L4 52966 S GROWTH HORMONE
L5 56694 S L1 OR L4
L6 1 S L2 AND L5
L7 10115 S SOMATOTROPIN
L8 57663 S L5 OR L7
L9 1 S L8 AND L2
L10 12 S GLYCINE-PROLINE-GLUTAMATE
L11 1 S L10 AND L8
L12 9 S L10 AND L2

113 51*
109* 34*
106 31*
105 19
103 11
100 7*
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91
90*
82
73
66
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55*